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COVID-19 infection in kidney transplant patients: Clinical experience of Baskent University Transplantation Department

Halil İbrahim Taşcı
Department of General Surgery, Faculty of Medicine, Başkent University, Ankara, Turkey

Abstract

Aim: The aim of our study was to present our clinical approach to patients who underwent kidney transplantation in our clinic and were diagnosed with coronavirus disease 2019 during their follow-up, and to examine factors affecting the course of the disease and mortality.

Material and Methods: The data of patients who underwent kidney transplantation in Baskent University Faculty of Medicine between March 2020 and August 2021 and who were diagnosed with the coronavirus disease 2019 were retrospectively analyzed. The patients included in the study were divided into two groups: deceased (Group 1) and survivors (Group 2). Parameters that may have an effect on mortality were statistically analyzed.

Results: Among the admission laboratory values of 43 patients included in the study, the albumin value was statistically significantly lower, while the ferritin value was higher in Group 1 ($p<0.05$). Positive culture results were statistically more frequent in the mortality group ($p<0.05$). The length of intensive care stay and the duration of intubation were longer in the mortality group.

Discussion: The coronavirus disease 2019 may have a more severe and fatal course in kidney transplant patients due to other underlying chronic diseases and immunosuppressive agents that have to be used. There is a need for large-scale multicenter clinical studies to establish standard guidelines for the treatment and reveal other factors affecting the course of the disease and mortality.

Keywords

Kidney Transplantation, Immunosuppressive, Coronavirus Disease 2019, Mortality

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Corresponding Author: Halil İbrahim Taşcı, Department of General Surgery, Faculty of Medicine, Başkent University, Ankara, Turkey.
E-mail: okcu6528@gmail.com P: +90 505 481 04 45
Corresponding Author ORCID ID: https://orcid.org/0000-0003-2269-4798
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Introduction

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory failure virus (SARS-COV-2) was first identified in Wuhan, China in December 2019 [1]. In January 2020, the World Health Organization declared COVID-19 a global public health emergency, and two months later, the coronavirus outbreak was declared a global pandemic [2]. Although the disease is known to be transmitted mainly via droplets or direct contact, it has also been reported to be transmitted indirectly through contaminated surfaces [3]. Elderly patients and those with comorbidities such as hypertension, diabetes mellitus, immune system disorders, respiratory or heart failure, chronic kidney disease, and cancer have been observed to have a more severe course [4].

The clinical symptoms, treatment, and prognosis of COVID-19 pneumonia in kidney transplantation patients are expected to differ greatly from the general population due to immunosuppressives that have to be used [5]. Considering their decreased T-cell immunity, transplant recipients are thought to be at a higher risk for bacterial and viral infections [6]. Although solid organ transplant patients infected with the respiratory syncytial virus, influenza viruses, parainfluenza virus, and adenoviruses have a poorer prognosis, such a result has not been seen in Middle East Respiratory Syndrome [7]. The available data on the course of COVID-19 in patients who had undergone solid organ transplantation and received immunosuppressive therapy are limited. The pandemic and all these uncertainties negatively affect the number of organ donations and organ transplants as well as the outpatient follow-up of patients who had previously undergone transplantation [8].

In this study, we aimed to present our clinical approach to the follow-up and treatment of patients who had previously undergone kidney transplantation in our clinic and were diagnosed with COVID-19 during their follow-up, and to examine the factors affecting the course of the disease and mortality.

Material and Methods

This study was approved by the Medical and Health Sciences Research Board of Baskent University (Project Date: 2021-06-01, No:KA21/271) and supported by Baskent University Research Fund. The data of patients who underwent kidney transplantation in Baskent University Faculty of Medicine, Department of Transplantation between March 2020 and August 2021 and who were diagnosed with COVID-19 during their follow-up and treated on an inpatient or outpatient basis were retrospectively analyzed. The study included patients with clinical findings of COVID-19 and a positive polymerase chain reaction (PCR) test result. All patients underwent posterior-anterior chest radiograph and chest computed tomography (CT). Bilateral peripheral consolidation and/or ground-glass opacity were considered lung involvement. The general approach of our transplantation discipline to altering immunosuppressive therapy was as follows:

- Not making any changes in the immunosuppressive therapy regimen of patients with a good clinical status,
- Continuing the same dose of steroids and cyclosporine, one of the calcineurin inhibitors, in all patients using these drugs,
- First reducing the dose of antimetabolite (mycophenolate) in patients with a worsening general condition or discontinuing it if the patient's general condition does not improve,
- Reducing the drug dose in patients using tacrolimus as a calcineurin inhibitor or mTOR inhibitor (everolimus or sirolimus) if the clinical status does not improve despite the revision of the antimetabolite dose given simultaneously or completely discontinuing the drug, if necessary,
- Increasing the immunosuppressive drugs of patients with a negative follow-up PCR test result and improved clinical findings to pre-COVID-19 doses.

A total of 43 patients who met the study criteria were evaluated. The patients included in the study were divided into two groups: deceased (Group 1) and survivors (Group 2). The effects of other parameters on mortality were statistically analyzed.

Statistical analysis

The analyses of the study were performed using the SPSS V21.0 software package. The level of significance was set at $p<0.05$ for all analyses. The normality distribution assumption of the data was evaluated using the Kolmogorov-Smirnov test. Categorical variables were presented as frequency tables, while numerical variables were presented as descriptive measures (mean ± standard deviation or median (min-max) in nonparametric cases). One-way analysis of variance (ANOVA) was used for inter-group comparisons when parametric conditions were provided, while the Kruskal-Wallis ANOVA method was used in other cases. Of the post-hoc, Tukey, Scheffe, and Tamhane tests, the appropriate one was preferred for pairwise comparisons. The student t-test or Mann-Whitney U test was used for two-group comparisons. The chi-square analysis was used to test whether categorical variables were correlated or not, while Pearson's or Spearman's correlation tests were used to determine the correlation between numerical variables.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Of the 43 patients included in the study, 17 (39.5%) were female and 26 (60.5%) were male, with a mean age of 48.51±13.90 years. Of the patients, 13 (30.2%) underwent kidney transplantation due to hypertension, 10 (23.3%) due to diabetes mellitus, 6 (14%) due to cryptogenic causes, 4 (9.3%) due to hereditary causes, and 10 (23.25%) underwent kidney transplantation due to other causes. While 16 (37.2%) patients had cadaveric transplantation, 27 (62.8%) patients had living-donor transplantation (8 from parents, 6 from siblings, 12 from spouses, 1 from other donors). As immunosuppressive therapy, 25 (58.1%) patients were using tacrolimus, mycophenolate mofetil, and prednisolone, 14 (32.6%) patients were using cyclosporine, mycophenolate mofetil, and prednisolone, and 3 (7%) patients were using sirolimus, mycophenolate mofetil, and prednisolone, while 1 (2.3%) patient initially used tacrolimus, mycophenolate mofetil, and prednisolone but was switched from tacrolimus to everolimus due to the side effects (Table 1). Twenty-three (53.5%) patients presented with cough, 18 (41.9%) patients with fever, 17 (39.5%) patients with fatigue, 11 (25.6%) patients with shortness of breath, and 9 (20.9%) patients presented with diffuse body pain complaint. The time

from transplantation to COVID-19 diagnosis was calculated and found to be 62.65±48.51 months. According to clinical findings, 30 (69.76%) patients were treated on an inpatient basis, 18 (60%) of whom required intensive care (with a median length of hospital stay of 12 (range, 1-86) days and a median length of intensive care stay of 9.5 (range, 2-57) days). All patients with a requirement for intensive care required intubation, with a duration of intubation of 6 (range, 1-28) days.

Patients were divided into two groups: deceased (Group 1) and survivors (Group 2), and parameters that could affect mortality were analyzed. The mortality group had a statistically significantly higher mean age than the other group (53.88±13.35 vs. 45±13.50 (p=0.039)). The two groups were similar in terms of gender distribution (p=0.27). None of the parameters such as the presence or absence of comorbid disease (hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease), pre-transplant hemodialysis history, right or left kidney transplantation, etiology of kidney failure, type of transplantation (living-donor or cadaveric), or donor type (parents, sibling, spouse, other) were found to have an effect on mortality (p>0.05). Although the time from transplantation to COVID-19 diagnosis was longer in Group 2 (64.80±47.93, 59.35±50.66), there was no statistically significant difference between the groups (p=0.172). The presence of a previous rejection attack had no effect on mortality during COVID-19 (p=0.41). Immunosuppressive agents used by patients before they were infected with COVID-19 were similar in both groups (p=0.72). The presenting complaints (fever, cough, fatigue, shortness of breath, diffuse body pain) were also similar in both groups (p>0.05). There was no significant difference between the groups in terms of hemoglobin, white blood cell, neutrophil, lymphocyte, neutrophil-to-lymphocyte ratio, C-reactive protein, fibrinogen, urea, creatinine, sodium, potassium, lactate dehydrogenase, D-dimer, alanine aminotransferase, aspartate aminotransferase values (p>0.05). The albumin value was significantly lower (p=0.04) but the ferritin value was significantly higher in Group 1 (p=0.029). Although the prevalence of involvement on chest CT was higher in the mortality group, there was no statistically significant difference between the groups (p=0.11). While there was growth in any of the cultures ordered for 12 (70.58%) of deceased 17 patients, only 1 (3.84%) of the survived patients had a positive culture result (p<0.001). All patients in Group 1 were admitted to the intensive care unit, but only 1 (3.84%) patient in Group 2 was admitted to the intensive care unit (p<0.001). The length of hospital stay was similar in both groups (p=0.89); however, the length of intensive care stay (p<0.001) and the duration of intubation (p <0.001) were significantly longer in Group 1. The antiviral agent preferred for the treatment and the antiaggregants/anticoagulants used were similar in both groups (p=0.24, p=0.60, respectively). The frequency of plasma use was significantly higher in Group 1 compared to Group 2 (p=0.006). Of the 13 patients who required hemodialysis during their treatment, only 2 (15.38%) survived, while 11 (84.61%) died (p<0.001). Of the 17 patients who required to use positive inotropes, 16 (94.11%) died and only 1 (5.88%) patient survived (p<0.001) (Table 2).

While the immunosuppressive agent used by the patients before COVID-19 infection did not have any effect on the length of hospital stay (p=0.31) and the length of intensive care stay (p=0.12), the duration of intubation was significantly longer in those using the combination of tacrolimus-mycophenolate mofetil and prednisolone (p=0.026). Revisions made in the immunosuppressive treatment regimen of COVID-19 patients were similar between the groups (p=0.14 for mycophenolate mofetil (unchanged/reduced/discontinued), p=0.29 for tacrolimus). No change was made in the cyclosporine dose. Revision of drug doses had no statistically significant effect on the length of hospital stay, length of intensive care, and duration of intubation (p>0.05). The changes made in the immunosuppressive dose are summarized in Table 3. The binary regression analysis showed that the presence of involvement on CT was effective in predicting the length of intensive care stay (p=0.026, R square=0.27).

As expected, the correlation analysis showed a positive correlation between the length of hospital stay, length of intensive care stay, and duration of intubation, and between the length of intensive care stay and duration of intubation (p<0.001). There was a positive correlation between mortality and age, length of intensive care stay, duration of intubation, hospital-acquired infection, positive culture, hemodialysis requirement during the disease, and positive inotropic drug requirement, and a negative correlation between mortality and albumin value (p<0.001).

Table 1. Comparative data of Group 1 and Group 2 before COVID-19.

	GROUP 1 (n=17)	GROUP 2 (n=26)	p value
Age (year)	53.88 ±13.35	45±13.35	0.039
Gender			
Female	5	12	0.27
Male	12	14	
Comorbid disease			
Yes	15	21	0.51
No	2	5	
Hemodialysis history			
Yes	12	19	0.77
No	5	7	
Etiology of renal failure			
Diabetes	5	5	0.57
Hypertension	7	6	
Others	5	15	
Kidney donor			
Alive	10	17	0.66
Cadaveric	7	9	
Immunosuppressive			
TACRO/MMF/PRED.	9	16	0.62
CYCLO/MMF/PRED.	6	8	
SIRO/MMF/PRED.	2	1	
EVERO /MMF/PRED.	0	1	
Rejection attack			
Yes	4	13	0.83
No	13	13	
Time between transplantation and diagnosis	59.35±50.66	64.80±47.93	0.72

MMF: mycophenolate mofetil, TACRO: tacrolimus, CYCLO: cyclosporine. EVERO: everolimus, SIRO: sirolimus, PRED: prednisolone.

Table 2. Comparative data of Group 1 and Group 2 during COVID-19.

	GROUP 1 (n=17)	GROUP 2 (n=26)	p value
Immune plasma adminisration			
Yes	6	1	0.006
No	11	25	
Antiviral			
No	1	4	0.24
Hydroxychloroquine	1	5	
Favipiravir	15	17	
Antiaggregant/coagulant			
No	2	6	0.6
LMWH	12	17	
Acetyl salicylic acid	3	3	
Positive Culture			
Yes	12	1	<0.001
No	5	25	
Hemodialysis requirement			
Yes	11	2	<0.001
No	6	24	
Positive inotropic requirement			
Yes	16	1	<0.001
No	1	25	
Tomographic lung involvement			
Yes	16	15	0.11
No	1	5	
Albumin (g/dL)	3.37±0.69	3.78±0.43	0.04
Ferritin (ng/ml)	770(129-4953)	313(57-4583)	0.008

LMWH: low molecular weight heparin

Table 3. Changes in immunosuppressive doses during COVID-19 treatment.

	GROUP 1 (n=17)	GROUP 2 (n=26)	p value
Mycophenolate			
Not changed	4	14	0.14
Reduced	6	6	
Stopped	7	6	
Tacrolimus			
Not changed	2	8	0.29
Reduced	4	6	
Stopped	3	2	
Cyclosporine			
Not changed	6	8	
Reduced	0	0	
Stopped	0	0	
Sirolimus			
Not changed	2	1	
Reduced	0	0	
Stopped	0	0	
Everolimus			
Not changed	0	0	
Reduced	0	1	
Stopped	0	0	

Twenty-six (60.46 %) patients who survived and were discharged were followed up regularly on days 15, 30, and then on a monthly basis. The median follow-up duration was calculated to be 2.5 (range, 1-8) months. The immunosuppressive therapies of patients with a negative follow-up PCR test result and improved clinical findings were increased to pre-COVID-19 doses, and their immunosuppressive drug levels were monitored based on routine practice. During the follow-ups, none of the patients had recurrent disease and all patients had normal renal functions.

Discussion

In kidney transplant patients, immune response, especially the T-cell response, is suppressed due to long-term use of immunosuppressive agents [5]. In addition to the immunosuppressive drugs used, these patients also have a high risk of COVID-19 due to their underlying chronic kidney failure and other comorbid diseases such as hypertension and diabetes mellitus [4]. Most studies have found a higher incidence of COVID-19 in kidney transplant patients compared to the normal population, with a more severe and fatal course [3,9]. Furthermore, it is believed that close follow-up of these patients will help in early diagnosis [9].

Some studies have suggested that immunosuppressed patients may not have an increased risk of COVID-19 compared to the normal population [10]. Supporting this hypothesis, the rates have not been found to be high although both a higher incidence of COVID-19 and mortality are expected in patients with post-transplant chronic immunosuppression [11]. This is interpreted as the ability of immunosuppressives to protect the patient against the dramatically increased proinflammatory cells due to COVID-19. Another hypothesis is that immunosuppressive therapy may also mitigate the viral cytopathic effect [11].

It has been found that post-transplant COVID-19 patients are mostly in their sixth decade of life, and the incidence is higher in men. Of the 43 patients included in our study, 17 (39.5%) were female and 26 (60.5%) were male, with a mean age of 48.51±13.90 years. The time from transplantation to diagnosis has usually been observed to be longer in patients diagnosed with COVID-19 [9]. In our study, the time from transplantation to COVID-19 diagnosis was calculated to be 62.65±48.51 months. Interestingly, an improvement in radiographic findings has been observed 7-10 days after the onset of symptoms without specific antiviral therapy [12]. Although there are approaches recommending high-resolution CT to monitor the course of pneumonia, there have been centers that do not include it in their routine practice, arguing that it is not necessary [4].

A study comparing COVID-19 patients with and without kidney transplantation who were hospitalized and treated showed that the average age of kidney transplant recipients was lower (7 years) and they had more comorbid disorders [13]. Similar to the general population, the most common symptoms in kidney recipients with COVID-19 have been reported as fever, myalgia, and cough [6]. The course of the disease can be quite different. Of our patients, 23 (53.5%) had cough, 18 (41.9%) had fever, 17 (39.5%) had fatigue, 11 (25.6%) had shortness of breath, and 9 (20.9%) had diffuse body pain complaint. Of the 43 patients diagnosed with COVID-19, 30 (69.76%) required hospitalization, and 13 (30.23%) recovered with outpatient follow-up. Kidney

transplant patients with COVID-19 infection have been found to have more impaired kidney functions than those who have not undergone transplantation. It is believed that this may be related to the presence of chronic renal failure in the history of kidney transplant patients as well as acute renal failure due to frequent diarrhea and elevated fever [13]. Moreover, it has been observed that kidney transplant patients with COVID-19 infection have a longer disease course with more severe symptoms due to the effect of immunosuppressive drugs used for a long time.

Other than supportive care, the management of COVID-19 patients has not yet been standardized. This also applies to other patients diagnosed with COVID-19 who had undergone solid organ transplantation. Especially during the adjustment of immunosuppressive therapy, the balance between acute rejection and infections that may be caused by bacterial and/or opportunistic pathogens should be maintained well [1]. The data on how to modify the dose of immunosuppressive drugs in transplant patients with COVID-19 is very limited. Some suggestions have been made on this subject [2, 11, 14]. There is no large-scale study investigating the efficacy of antiviral agents on solid organ transplant patients. The data obtained so far support that only remdesevir has a positive effect on the course of the disease in patients with severe COVID-19 who had undergone solid organ transplantation [15]. Although there are studies showing that the use of convalescent plasma contributes positively to the course of the disease in COVID-19 patients with solid organ transplantation, most of them are case reports [15,16]. In our study, the antiviral and immune plasma treatment option changed in parallel with the changes in the algorithms over time.

Limitations of the study

The limitations of the study are collecting the data from patient records and the absence of objective examination findings due to the retrospective nature of the study.

Conclusion

There is very limited data on how to manage immunosuppressive agents during the follow-up of these patients and on the efficacy of other treatment alternatives. Furthermore, there are many unknowns regarding other parameters that may affect the course of the disease and mortality. Although some parameters that may be associated with mortality were determined in our study, the small sample size, the lack of standard approaches to diagnosis and treatment, and the single-center design of the study prevented us from stating strong conclusion sentences. There is an urgent need for large-scale multicenter clinical studies to eliminate all these negativities, establish standard guidelines for treatment, and reveal other factors affecting mortality and the course of the disease.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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